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Τίτλος : «Αξιολόγηση της ποιότητας αναφοράς  
Τυχαιοποιημένων Κλινικών Δοκιμών σε ασθενείς με Χρόνια  
Λεμφοκυτταρική Λευχαιμία που λαμβάνουν ως θεραπεία  
ibrutinib, obinutuzumab, idelalisib, ή venetoclax στο διάστημα  
2010-2018 με τη χρήση της δοκιμασίας CONSORT.»

Title: “Assess the reporting quality of Randomized controlled  
clinical trials for ibrutinib, obinutuzumab, idelalisib, or  
venetoclax in Chronic Lymphocytic Leukemia published from  
2010 to 2018 using the CONSORT statement”

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## A. ΠΕΡΙΛΗΨΗ

Η χρόνια λεμφοκυτταρική λευχαιμία (ΧΛΛ) ορίζεται ως μια κλωνική λεμφοϋπερπλαστική διαταραχή των Β- λεμφοκυττάρων . Η διαταραχή αυτή χαρακτηρίζεται από τη συσσώρευση λεμφοκυττάρων στο μυελό των οστών , στο περιφερικό αίμα αλλά και στους λεμφαδένες και τον σπλήνα. Πρόκειται για νόσο των μεγάλων ηλικιών ( συνήθης συχνότητα εμφάνισης μετά τα 70 έτη ) , με διπλάσιο επιπολασμό στο άρρεν φύλο , ενώ συγχρόνως αποτελεί τη συχνότερη μορφή λευχαιμίας στις χώρες του Δυτικού κόσμου. Σημαντικό βήμα στην θεραπευτική αντιμετώπιση της ΧΛΛ αποτέλεσε η χρήση των αναστολέων σηματοδοτικών οδών , των αντι- BCL2 και των αντι-CD20 αντισωμάτων. Πρόκειται για τα νέα θεραπευτικά χημειοφάρμακα ibrutinib, obinutuzumab, idelalisib, και venetoclax. Οι τυχαιοποιημένες ελεγχόμενες κλινικές δοκιμές (RCTs) αποτελούν το πιο αξιόπιστο μέσο για την αξιολόγηση της αποτελεσματικότητας των κλινικών παρεμβάσεων . Η μέθοδος CONSORT (Consolidated Standards of Reporting Tests) είναι μια προσέγγιση που βασίζεται στην τεκμηρίωση για τη βελτίωση της ποιότητας της υποβολής εκθέσεων σχετικά με τυχαιοποιημένες ελεγχόμενες κλινικές μελέτες. Σκοπός της παρούσας μελέτης είναι η αξιολόγηση της ποιότητας των δημοσιευμένων RCTs σχετικά με τη χρήση των ibrutinib, obinutuzumab, idelalisib, και venetoclax για τη θεραπεία της ΧΛΛ, σύμφωνα με τη λίστα CONSORT.

Λέξεις κλειδιά: CONSORT, Τυχαιοποιημένες ελεγχόμενες κλινικές δοκιμές , Ibrutinib, Obinutuzumab, Idelalisib, Venetoclax, Χρόνια λεμφοκυτταρική λευχαιμία .

Εισαγωγή: Οι τυχαία ελεγχόμενες κλινικές δοκιμές (RCTs) είναι το πιο αξιόπιστο εργαλείο για την αξιολόγηση της αποτελεσματικότητας των κλινικών παρεμβάσεων. Τα Ενοποιημένα Πρότυπα Δοκιμών Αναφοράς (CONSORT) είναι μια προσέγγιση που βασίζεται σε τεκμηρίωση για τη βελτίωση της ποιότητας των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών.

Στόχος: Η αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών που δημοσιεύτηκαν από το 2010 έως το 2018 και αναφέρονται σε ασθενείς με ΧΛΛ οι οποίοι έλαβαν ως θεραπεία οποιοδήποτε από τα νεότερα φάρμακα χημειοθεραπείας- ibrutinib, obinutuzumab, idelalisib και venetoclax - . Η αξιολόγηση έγινε χρησιμοποιώντας τη λίστα CONSORT.

Μέθοδοι: Στο PubMed έγινε αναζήτηση τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών - δημοσιευμένες στην αγγλική γλώσσα- που περιελάμβαναν ασθενείς με χρόνια λεμφοκυτταρική λευχαιμία οι οποίοι έλαβαν ως θεραπεία ένα από τα ακόλουθα φάρμακα ibrutinib, obinutuzumab, idelalisib και venetoclax. Οι δοκιμές θεωρήθηκαν επιλέξιμες όταν οι συμμετέχοντες είχαν εκχωρηθεί τυχαία σε τουλάχιστον δύο ομάδες θεραπείας. Η ποιότητα της αναφοράς αξιολογήθηκε με τη χρήση ερωτηματολογίου 25 θέσεων βάσει της λίστας ελέγχου CONSORT. Τα άρθρα ομαδοποιήθηκαν σε δύο χρονικές περιόδους (πριν και μετά το 2016) και στατιστικά συγκρίθηκαν για την πληρότητα των ερωτημάτων της λίστας CONSORT.

Αποτελέσματα: Η αναζήτηση εντόπισε 18 κατάλληλα άρθρα για ανάλυση. Η πληρότητα των ερωτημάτων της δήλωσης CONSORT είναι μεγαλύτερη από το 75% σε 13 μόνο ερωτήματα από το σύνολο 37 που περιέχει τη λίστα. Σε 10 ερωτήματα το ποσοστό κάλυψης

ερωτημάτων είναι μικρότερο από 50%. Με την πάροδο του χρόνου, σημειώθηκε βελτίωση στη δομή καθώς και την παρουσίαση των RCTs.

Συμπεράσματα: Η ποιότητα της υποβολής RCTs με επίκεντρο τη χρόνια λεμφοκυτταρική λευχαιμία σε θεραπευόμενους που λαμβάνουν αναστολείς των σηματοδοτικών οδών, αντι-BCL2 ή αντι-CD20, παρουσιάζει βελτίωση με την πάροδο του χρόνου εξακολουθώντας ωστόσο να παραμένει μη ικανοποιητική. Απαιτείται περαιτέρω βελτίωση της υποβολής εκθέσεων για την αξιολόγηση της εγκυρότητας της κλινικής έρευνας.

## ABSTRACT

The definition of chronic lymphocytic leukemia (CLL) refers to a clonal lymphoproliferative disorder of B lymphocytes. This disorder is characterized by the accumulation of lymphocytes in the bone marrow, peripheral blood, but also in the lymph nodes and the spleen. This is a disease of the elderly (normal incidence after 70 years), with a double prevalence in male gender. While at the same time is the most common form of leukemia in the Western world. An important step in the treatment of CLL was the use of inhibitors of signal transduction pathways, anti-BCL 2 and anti-CD20 antibodies. These are the new therapeutic drugs ibrutinib, obinutuzumab, idelalisib, and venetoclax. Randomized controlled clinical trials (RCTs) are the most reliable tool for assessing the effectiveness of clinical interventions. The Consolidated Standards of Reporting Tests (CONSORT) is an approach based on documentation to improve the quality of reporting on randomized controlled clinical trials. The purpose of this study is to evaluate the quality of published RCTs regarding the use of ibrutinib, obinutuzumab, idelalisib, and venetoclax for the treatment of CLL, according to the CONSORT list.

KEY WORDS : CONSORT, Randomized Controlled Trials, Quality, Ibrutinib, Obinutuzumab, Idelalisib, Venetoclax, Chronic Lymphocytic Leukemia, Methodology.

Background: Randomized controlled clinical trials (RCTs) are the most reliable tool for assessing the effectiveness of clinical interventions. The Consolidated Standards of Reporting Tests (CONSORT) is an approach based on documentation to improve the quality of reporting on randomized controlled clinical trials.

Objectives: Assess the reporting quality of RCTs for treatment for CLL, in patients who received any of the new chemotherapy drugs- ibrutinib, obinutuzumab, idelalisib, and venetoclax - published from 2010 to 2018 using the CONSORT statement

Methods: PubMed was searched for English-language RCTs involving patients with Chronic Lymphocytic Leukemia and who received one of the following drugs as a treatment- ibrutinib, obinutuzumab, idelalisib, and venetoclax-. Trials were considered eligible when

participants were randomly assigned to at least two treatment arms. Quality of reporting was assessed using a 25-item questionnaire based on the CONSORT checklist. The articles were grouped in two time periods (before and after 2016) and statistically compared to the completeness of the CONSORT statement.

Results: The search identified 18 eligible articles for analysis. Completeness of CONSORT statement questions greater than 75% occurs in 13 only queries from the total 37 that contains the list. In 10 queries the query coverage rate is less than 50%. Over time, there has been an improvement in the construction and presentation of RCTs.

Conclusions: Quality of reporting in RCTs focusing on chronic lymphocytic leukemia and treatment with new TKIs is showing improvement over time, but still remains unsatisfactory. Further improvement of reporting is necessary to assess the validity of clinical research.

## B.INTRODUCTION

With the advancement of technology, any new medical achievement is made available to any part of the world through its publication in world medical sites, providing a strong knowledge for every treating physician. The use of randomized clinical trials minimizes the bias in the efficacy of the therapeutic effects of each new drug. Randomized clinical trials have contributed to results free of bias[1,2,7,8]. In this way they contributed catalytically to improving the quality of therapeutic interventions, bringing more favorable results to patients. For these reasons, randomized studies have the highest placement among clinical trials [3,4,5,6].

However, a great deal of medical information and clinical studies are available in a number of online biomedical journals, many of which are not based on detailed descriptions. Important information about the design of the study, patient participation criteria, specimen randomization method and other clarification details are often bypassed and not mentioned. Ambiguities and inaccuracies generate concerns and questions to the reader [9,10,11].

In addition, it is known that most RCTs are conducted with funding from the pharmaceutical companies concerned. So we understand that information about industries and sources of finance is absolutely necessary. Thus eliminating suspicions of feasibility.

In order to limit bias in randomized clinical trials, the CONSORT statement was published in 1996 [12]. The use of the CONSORT list is related to improving the quality of RCTs. The revised CONSORT statement consists of 25 questions which are classified into 6 categories. At the same time, a four-step flow chart is included. So we understand the use of the CONSORT statement as a guide for recording more complete and properly structured randomized clinical trials [13-17].

This study evaluated the randomized clinical trials concerning the treatment of chronic lymphocytic leukemia using the novel inhibitors, anti-BCL2 and anti-cd20 antibodies [22-25,33]. In the field of hematopoietic malignancies the evaluation of clinical trials is limited. We chose chronic lymphocytic leukemia and treatment with the newer drugs belonging to inhibitors of signal transduction pathways, anti-BCL2 and anti-cd20 antibodies [30-32] as the latter became more prevalent in the treatment of CLL [26-29]. So as their use becomes more and more extensive, the concerns about efficacy and side effects in real world data patients also increase.

## C. METHODS

### Data Sources, Search Strategies and Studies Selection

PubMed was used as a data source. There was the search of randomized clinical trials involving the treatment of CLL in the period 2010-2018. In PubMed, we used as filters the "Randomized Controlled Trial" type of article and "English" language. Then, as a search criterion we used the combination of the following terms: "Chronic lymphocytic leukemia", "CLL", "ibrutinib", "obinutuzumab", "idelalisib", "venetoclax", "inhibitors of signal transduction pathways", "tyrosine kinase inhibitors", "anti-BCL2" and "anti-CD20". The trials were eligible if the participants were randomly assigned to at least two groups with a different treatment strategy for each group. At least one of the groups should be used as a therapeutic drug of the following: idelalisib, ibrutinib, venetoclax or obinutuzumab.

### Data Extraction and Reporting Assessment Tool

As assessment tool for quality of reporting, we used the revised CONSORT checklist, which includes a 25-item questionnaire. CONSORT statement includes 25-item checklist with sub-items (total 37 items).

We clarify that the criteria of the CONSORT statement in order to create a randomized clinical trial requires the randomization of patients into categories by randomization. Separation should be blinded and interventions similar in the groups of patients. In addition, the criteria of the CONSORT list include the creator of the random distribution as well as the mechanism applied for random separation. Finally, reference is also made to the persons who recorded the results.

### Methodological Evaluation

We evaluated 18 randomized clinical trials associated with the treatment of CLL in patients where receiving any of newer therapeutic drugs ibrutinib, obinutuzumab, idelalisib, and venetoclax. The tests took place over the period 2010-2018 which coincided with the development of novel inhibitors, anti-BCL2 and anti-CD20 antibodies. Data was imported into tables using the Microsoft Excel 2010 program. Unclear or alternative answers (except

yes or no) were recorded as negative responses. Only explicit references were included in the positive responses.

The studies were divided into two categories depending on whether they were published before or after 2016. This chronological separation is due to the fact that the majority of studies related to novel inhibitors, anti-BCL2 and anti-CD20 have been published over the last two years. The purpose of this separation was to assess the quality and validity of the trials [18-20].

The SPSS statistical program was used and the two groups were compared according to the CONSORT statement. For the comparison of the two groups a chi-squared test was applied with the use of Weight Cases. The coverage ratios of the CONSORT list queries were calculated for each time period according to the separation, as well as the overall rates for 2010-2018. Also, the P value was calculated for each of the comparisons. (Table 1).

#### D. RESULTS

A total of 2631 potentially eligible references were identified (Fig. 1), of which 1579 were measured in the searching of another myeloid malignancy.

Of the remaining 1052 articles, 1034 were rejected. The blockade is due to the fact that 692 articles were not relevant to us. In particular, these were reported in other haematological malignancies such as lymphomas, mantle lymphoma and B cell lymphoma. 340 articles were rejected as they showed non-randomized studies. Cohort studies as well as case control studies were included in this last category. In addition, two articles referring to experimental models in an animal population were excluded.

So, finally, we ended up with 18 articles that were about our issue. These articles include randomized clinical trials and articles which describe randomized clinical trials. All of the material refers to the use of venetoclax, ibrutinib, idelalisib and obinutuzumab in the treatment of CLL patients.

#### Main Results

Of the 18 articles studied, 7 were published in the period 2010-2016 and 11 were between 2017-2018. Table 1 shows the frequency of coverage of the CONSORT list queries in both the overall study period and sub-categories. The 37 queries in the list include questions about the title of each article, for example, if the study characterized randomized or not. References are then made to the scientific background of the study and to the methods

applied to carry out a randomized trial (randomization method, blinded sample, statistical methods). To control the effectiveness of the study, questions are included about the number of participants, their characteristics, course or discontinuation of the study, and the outcomes for each group. Finally, there is discussion on the interpretation and generality of the results, while information on sources of funding and registration protocols is also provided.

In our study of questions such as Scientific background and explanation of rationale, Specific objectives or hypotheses and Generalisability, we observe full coverage in all studies. Higher occupancy rates of 83% to 94% are presented in questions such as : 3a. Description of trial design (such as parallel, factorial) including allocation ratio, 4a. Eligibility criteria for participants, 4b. Settings and locations where the data were collected, 5. The interventions for each group with sufficient details to allow replication, including how and when they were actually administered, 13a. For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, 18. Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory, 19. All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) and 25. Sources of funding and other support (such as supply of drugs), role of funders.

Percentages ranging from 50% to 77% are observed in queries about sample size (7a, 7b), type of randomization (8b), (11b), additional analyses (12b), losses and exclusions of each group (13b), dates (14a), estimated numbers and outcomes (16,17a, 17b), interpretations - entries and protocols (22,23,24).

Percentages smaller than 50% are observed in questions about the presentation of a structured study summary (1b), references to changes in methods and outcomes (3b, 6b), references to the method and how to create random distribution (8a, 10), early termination of the study (14b) and presentation of a table with the characteristics of the participants (15). These questions are covered at rates 27% to 44%.

The smallest percentages are observed in the questions about the concealment mechanism of the distribution (9) and the determination of the blind (11a). Rates are 16% and only 11% respectively.

#### Period Effect

By comparing the two time periods we set (according to the results of Table 1), there is a significant improvement in 6 thematic sections of the CONSORT statement. The most important improvement is observed in the 24th query, which refers to the study protocol with p value equal to 0.001. A significant improvement is also noted in the questions about the method of random distribution of the participants (8a), the statistical methods which used (12a) and the reports on termination or discontinuation of the study (14b). In these queries the p value equals 0.01. A final difference is also observed in questions 1b on the

structured summary of study design (p value 0.02) as well as in question 23 concerning the entry in the test record (p value 0.06).

## DISCUSSION

Our study in the field of randomized clinical trials in patients with CLL receiving any of the newer drugs - idelalisib, ibrutinib, venetoclax or obinutuzumab - as a treatment reveals that essential thematic aspects of RCTs are often overlooked and not mentioned. These omissions often cause concerns to the reader, making it difficult for them to assess the validity of the results.

Over the course of time, and especially in the last two years, there has been a significant improvement in the structure of RCTs. Fields such as the summary of the design of the trial, the description of the randomization methods, the description of the statistical methods, and reports on the termination or discontinuation of the study are now more detailed and accurate. Significant progress is made in presenting information on the study protocol, which is now more emphasized.

Similar studies performed to test RCTs reliability in hematological malignancies such as lymphomas [20], acute myeloid leukemia, chronic myeloid leukemia, and myelodysplastic syndromes [21] show unsatisfactory results to cover the queries of the CONSORT list.

Here we have to mention the limitations of our own study. In our study we evaluated articles published in PubMed. This choice was made as PubMed is the most commonly used medical database. Medical databases such as Cochrane Collaboration, SCOPUS, Embase, Web of Science, Clinical Trials and Clinical Trials Registry have not been studied. In addition, English was used as a language, and only articles in English were studied, which may contribute to bias.

In conclusion, our results for RCTs in CLL patients receiving idelalisib, ibrutinib, venetoclax or obinutuzumab show that RCTs do not fully conform to the CONSORT statement guidelines. We often see information being skipped while questions of the CONSORT statement remain unanswered. However, over time, there has been an improvement in the structure and presentation of RCTs. We hope they will become even more credible in order to eliminate any concerns about the reliability and validity of the results in the future

## Abbreviations and Acronyms

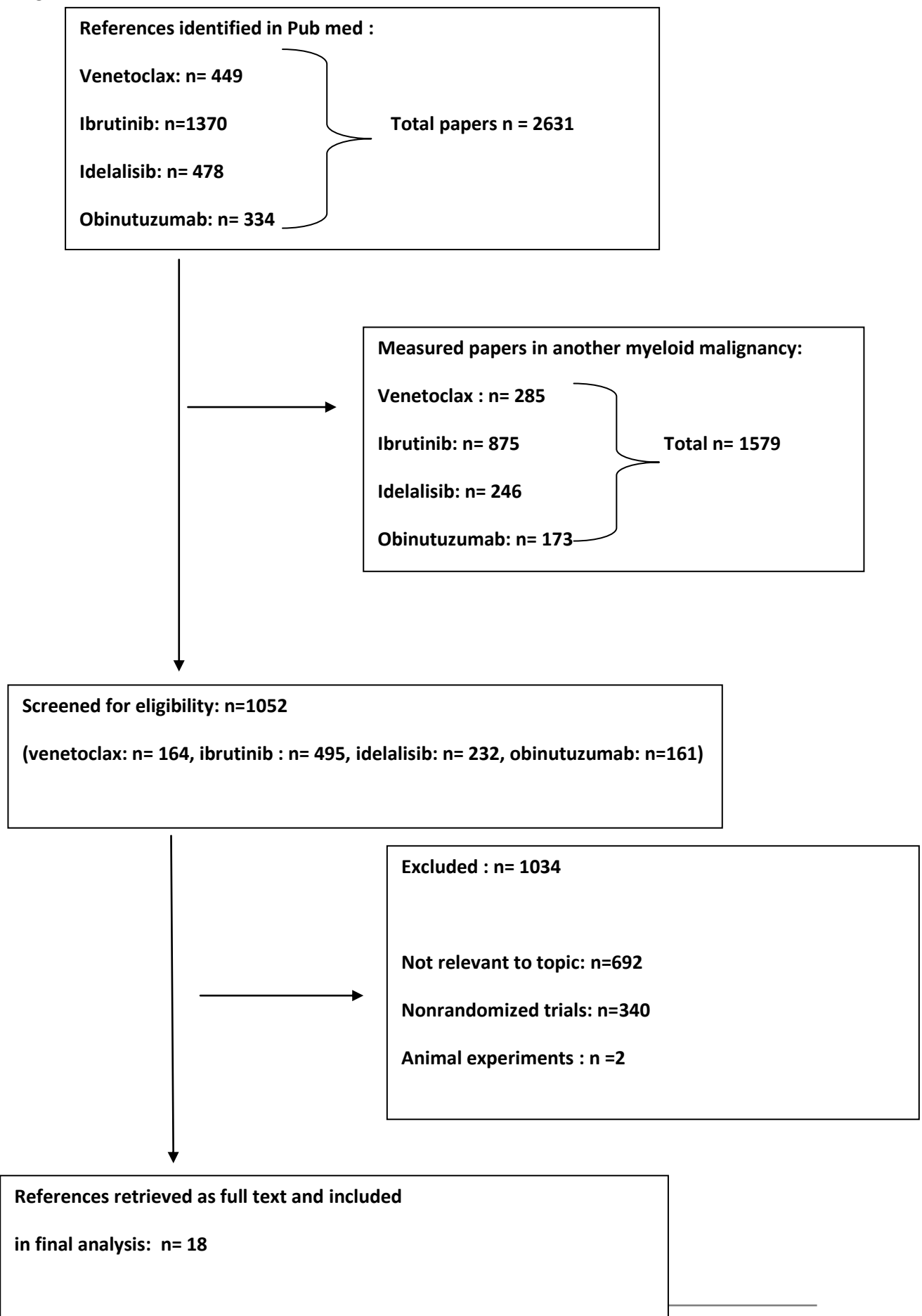
CLL	Chronic lymphocytic leukemia
RCTs	Randomized Controlled Trial
CONSORT	Consolidated Standards of Reporting Trials
SPSS	Statistical Package for the Social Sciences



Table 1.

Data items	Combined 2010-2018 (n=18)	Combined 2010-2016 (n=7)	Combined 2017-2018 (n=11)	P value
ABSTRACT / TITLE				
1a	0.16	0.00	0.27	0.13
1b	0.44	0.00	0.72	0.02
INTRODUCTION				
2a	1.00	1.00	1.00	-
2b	1.00	1.00	1.00	-
METHODS				
3a	0.88	0.85	0,90	0.73
3b	0.33	0.14	0,45	0.17
4a	0.88	0.85	0,90	0.73
4b	0.94	0.85	1,00	0.19
5	0.83	0.71	0,90	0.28
6a	0.66	0.71	0,63	0.73
6b	0.27	0.00	0,36	0.07
7a	0.50	0.42	0,54	0.62
7b	0.77	0.71	0,81	0.60
8a	0.33	0.00	0,54	0.01
8b	0.61	0.42	0,72	0.20
9	0.16	0.00	0,27	0.13
10	0.38	0,14	0,54	0.08
11a	0.11	0.00	0,18	0.23
11b	0.61	0,57	0,63	0.78
12a	0.50	0,14	0,72	0.01
12b	0.61	0,42	0,72	0.20
RESULTS				
13a	0.83	0.71	0,90	0.28
13b	0.61	0.42	0,72	0.20
14a	0.77	0.71	0,81	0.60
14b	0.33	0.00	0,54	0.01
15	0.33	0,28	0,36	0.73
16	0.55	0,28	0,72	0.06
17a	0.72	0,71	0,72	0.95
17b	0.72	0,71	0,72	0.95
18	0,83	0,71	0,90	0.28
19	0,88	1,00	0,81	0.23
DISCUSSION				
20	0,66	0,71	0,63	0.73
21	1,00	1,00	1,00	-
22	0,55	1,00	0,90	0.41
OTHER INFORMATION				
23	0.55	0,28	0,72	0.06
24	0.61	0,14	0,90	0.001
25	0.83	0,71	0,90	0.28

Figure 1.



## REFERENCES

1. Pfeifer M, Snodgrass GL. The continued use of retracted invalid scientific literature. *JAMA*. 1999;263:1420–1423.
2. Olkin I. Meta-analysis: reconciling the results of independent studies. *Stat Med*. 1995;14:457–472
3. Nystrom L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* (London, England). 1993; 341: 973-8.
4. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ*. 1996;313:570–571.
5. Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. *Int J Technol Assess Health Care*. 1996;12:195–208
6. Djulbegovic B, Loughran T, Hornung CA, Kloecker G, Efthimiadis EN, Hadley TJ, et al. The quality of medical evidence in hematology-oncology. *Am J Med*. 1999;106:198–205.
7. Pfeifer MP and Snodgrass GL. The continued use of retracted, invalid scientific literature. *Jama*. 1990; 263: 14203.
8. Olkin I. Meta-analysis: reconciling the results of independent studies. *Statistics in medicine*. 1995; 14: 457-72.
9. Schulz KF, Chalmers I, Hayes RJ and Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama*. 1995; 273: 408-12.
10. Juni P, Altman DG and Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* (Clinical research ed). 2001; 323: 42-6.
11. Liberati A, Himel HN and Chalmers TC. A quality assessment of randomized control trials of primary treatment of breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1986; 4: 942-51
12. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA*. 1996;276:637–639.
13. Schulz KF, Altman DG and Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC medicine*. 2010; 8: 18.
14. Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *The Cochrane database of systematic reviews*. 2012; 11: Mr000030.
15. Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA*. 2001;285:1987–1991
16. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al.; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134: 663–694.

17. Moher D, Schulz KF, Altman DG; CONSORT GROUP (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med*. 2001;134:657–662.
18. Moher D, Jones A, Lepage L. Use of the CONSORT Statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA*. 2001;285:1992–1995.
19. Moher D, Jones A, Lepage L. Use of the CONSORT Statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA*. 2001;285:1992–1995.
20. Kober T, Trelle S, Engert A. Reporting of Randomized Controlled Trials in Hodgkin Lymphoma in Biomedical Journals. *J Natl Cancer Inst*. 2006;98:620–625.
21. Ziogas DC, Zintzaras E. Analysis of the quality of reporting of randomized controlled trials in acute and chronic myeloid leukemia, and myelodysplastic syndromes as governed by the CONSORT statement. *Ann Epidemiol*. 2009 Jul;19(7):494-500.
22. Patel VM, Balakrishnan K, Douglas M, Tibbitts T, Xu EY, Kutok JL et al. Duvelisib treatment is associated with altered expression of apoptotic regulators that helps in sensitization of chronic lymphocytic leukemia cells to venetoclax (ABT-199). *Leukemia*. 2017 Sep;31(9):1872-1881.
23. Lampson BL, Davids MS. The Development and Current Use of BCL-2 Inhibitors for the Treatment of Chronic Lymphocytic Leukemia. *Curr Hematol Malig Rep*. 2017 Feb;12(1):11-19.
24. Shustik C, Bence-Bruckler I, Delage R, Owen CJ, Toze CL, Coutre S. Advances in the treatment of relapsed/refractory chronic lymphocytic leukemia. *Ann Hematol*. 2017 Jul;96(7):1185-1196.
25. Seiter K, Mamorska-Dyga A. Obinutuzumab treatment in the elderly patient with chronic lymphocytic leukemia. *Clin Interv Aging*. 2015 Jun 12;10:951-61.
26. Oughton JB, Collett L, Howard DR, Hockaday A, Munir T, McMahon K. GA101 (obinutuzumab) monoclonal Antibody as Consolidation Therapy In CLL (GALACTIC) trial: study protocol for a phase II/III randomised controlled trial. *Trials*. 2017 Jul 26;18(1):353.
27. Sanford DS, Wierda WG, Burger JA, Keating MJ, O'Brien SM. Three newly approved drugs for chronic lymphocytic leukemia: incorporating ibrutinib, idelalisib, and obinutuzumab into clinical practice. *Clin Lymphoma Myeloma Leuk*. 2015 Jul;15(7):385-91.
28. Owen CJ, Stewart DA. Obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia: overview and perspective. *Ther Adv Hematol*. 2015 Aug;6(4):161-70.
29. Hill BT, Kalaycio M. Profile of obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia. *Onco Targets Ther*. 2015 Aug 31;8:2391-7.
30. Ryan CE, Sahaf B, Logan AC, O'Brien S, Byrd JC, Hillmen P., et al. Ibrutinib efficacy and tolerability in patients with relapsed chronic lymphocytic leukemia following allogeneic HCT. *Blood*. 2016 Dec 22;128(25):2899-2908.

31. Davids M. , Brown J Ibrutinib: a first in class covalent inhibitor of Bruton's tyrosine kinase. *Future Oncol.* 2014 May;10(6):957-67.
32. Cramer P, von Tresckow J, Bahlo J, Engelke A, Langerbeins P, Fink AM et al. CLL2-BXX Phase II trials: sequential, targeted treatment for eradication of minimal residual disease in chronic lymphocytic leukemia. *Future Oncol.* 2018 Mar;14(6):499-513.
33. Chen RW, Palmer JM, Tomassetti S, Popplewell LL, Alluin J, Chomchan P, et al. Multi-center phase II trial of bortezomib and rituximab maintenance combination therapy in patients with mantle cell lymphoma after consolidative autologous stem cell transplantation. *J Hematol Oncol.* 2018 Jun 28;11(1):87.